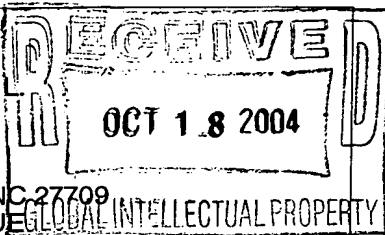


1 PM / BED

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:	
DEPPENBROCK, Bonnie GLAXOSMITHKLINE Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709 ETATS-UNIS D'AMERIQUE	

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference PU5004WO		IMPORTANT NOTIFICATION	
International application No. PCT/US 03/39740	International filing date (day/month/year) 12.12.2003	Priority date (day/month/year) 13.12.2002	
Applicant SMITHKLINE BEECHAM CORPORATION et al.			

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.


4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Ambroa, J.R. Tel. +49 89 2399-8012
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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference PU5004WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA416)	
International application No. PCT/US 03/39740	International filing date (day/month/year) 12.12.2003	Priority date (day/month/year) 13.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D451/02		
Applicant SMITHKLINE BEECHAM CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17.06.2004	Date of completion of this report 12.10.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lauro, P Telephone No. +49 89 2399-8288



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/39740**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-75 as originally filed

Claims, Numbers

1-42 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/39740**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ claims Nos.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-42 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-42
Inventive step (IS)	Yes: Claims	
	No: Claims	1-42
Industrial applicability (IA)	Yes: Claims	1-25,31-39
	No: Claims	26-30,40-42

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/39740

Re Item III

1. The examination is limited to the part of the application which has been searched, namely those parts relating to compounds of formula (I) in which B-R1 represents 6-phenyl-1,3-oxazinanyl or 2-phenyl morpholinyl (i.e. R1 is phenyl) which are supported by the examples.

Re Item V

2. Reference is made to the following documents:

- D1: WO 00/58292 A (SANOFI-SYNTHELABO) 5 October 2000 (2000-10-05)
D2: WO 96/23787 A (SANOFI) 8 August 1996 (1996-08-08)
D3: WO 02/094821 A (SANOFI-SYNTHELABO) 28 November 2002 (2002-11-28)
D4: EDMONDS-ALT ET AL.: THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 303, no. 3, 2002, pages 1171-79, XP002280312
D5: ALI ET AL.: BIOORG. MED. CHEM. LETT., vol. 11, 2001, pages 819-822, XP002280313
D6: NISHI ET AL.: BIOORG. MED. CHEM. LETT., vol. 10, 2000, pages 1665-68, XP002280314
D7: JP 01 031570 A (SANKYO) 1 February 1989 (1989-02-01)
D8: WO 02/079194 A (SCHERING CORP) 10 October 2002 (2002-10-10)
D9: WO 02/05819 A (BONDINELL WILLIAM E ;SMITHKLINE BEECHAM CORP (US); NEEB MICHAEL J) 24 January 2002 (2002-01-24)
D10: PALANI A ET AL: 'Discovery of 4-[(Z)-(4-Bromophenyl)-(ethoxyimino)methyl]-1'-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine N-Oxide (SCH 351125): An Orally Bioavailable Human CCR5 Antagonist for the Treatment of HIV Infection' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 44, no. 21, 11 October 2001 (2001-10-11), pages 3339-3342, XP002220286 ISSN: 0022-2623
D1: WO 00/58292 A (SANOFI-SYNTHELABO) 5 October 2000 (2000-10-05)
D2: WO 96/23787 A (SANOFI) 8 August 1996 (1996-08-08)
D3: WO 02/094821 A (SANOFI-SYNTHELABO) 28 November 2002 (2002-11-28)
D4: EDMONDS-ALT ET AL.: THE JOURNAL OF PHARMACOLOGY AND

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/39740

- EXPERIMENTAL THERAPEUTICS, vol. 303, no. 3, 2002, pages 1171-79, XP002280312
- D5: ALI ET AL.: BIOORG. MED. CHEM. LETT., vol. 11, 2001, pages 819-822, XP002280313
- D6: NISHI ET AL.: BIOORG. MED. CHEM. LETT. , vol. 10, 2000, pages 1665-68, XP002280314
- D7: JP 01 031570 A (SANKYO) 1 February 1989 (1989-02-01)
- D8: WO 02/079194 A (SCHERING CORP) 10 October 2002 (2002-10-10)
- D9: WO 02/05819 A (BONDINELL WILLIAM E ;SMITHKLINE BEECHAM CORP (US); NEEB MICHAEL J) 24 January 2002 (2002-01-24)
- D10: PALANI A ET AL: 'Discovery of 4-[(Z)-(4-Bromophenyl)-(ethoxyimino)methyl]-1'-[(2,4-dimethyl-3-pyridinyl)carbonyl]-4'-methyl-1,4'-bipiperidine N-Oxide (SCH 351125): An Orally Bioavailable Human CCR5 Antagonist for the Treatment of HIV Infection' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 44, no. 21, 11 October 2001 (2001-10-11), pages 3339-3342, XP002220286 ISSN: 0022-2623
- D11: WO 02/081449

3. Novelty

The subject-matter of claim 1 and dependent claims is anticipated by the disclosure of D1 through D7. Novelty is not acknowledged.

4. Inventive step

The problem underlying the present application appears to reside in the provision of compounds useful in the treatment of CCR5-related diseases and disorders.

The same activity is shown by the compounds disclosed in D8 to D11 which mainly differ from the compounds of the present application in the presence of a piperidine ring in the place of a morpholino ring. In view of the teaching of the prior art there appears to be no fixed structure in this class of compounds; the only features in common with all the active CCR5 antagonists disclosed in the above cited prior art appears to be a series of two heterocyclic rings linked by a group which may vary in structure. Since the compounds of the present application appears to show the essential elements (i.e. 2 heterorings variably linked via a group X), their activity would have been expected. In the absence of data which show unexpected effects for the compounds of the present application compared to the structurally closest compounds of the prior art, inventive step cannot be acknowledged.

**INTERNATIONAL PRELIMINARY
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International application No. PCT/US 03/39740

5. Claims 26-30,40-42 are directed to a method for treatment.